REMARKS

The applicants and their attorney thank the examiner for the courtesies extended during a telephone interview with Dr. Wu and Mr. Richards on January 14. The subjects discussed are set out in the Examiner's Interview Summary of January 21. During that interview, the degree of support needed and provided for claims to particular conditions and the support for a definition of R^1 and R^2 jointly forming methylene were discussed. It was suggested that so far as the former is concerned, the term "organ failure" should be tied more closely to the data included in the application. So far as the latter is concerned, it was pointed out that this value was that which would result in the simplest possible heterocycle being formed (this term being clearly supported) and that there was exemplification of this value in the compounds described at page 35 lines 23 and 31.

In response to the examiner's comments, claims 10 and 33, and in claim 14 utilities of organ failure or pulmonary fibrosis, have been deleted, but that of ulcerative colitis reinstated.. In view of the comments made during the telephone interview, the nature of the organ damage (i.e. liver, lung and kidney damage) referred to in claims 18 and 60 has been specified to be the result of over production of TNF-α or superoxide anion radicals, In claims 31, 46 and 54, reference to organ damage has been deleted Te claims specify the conditions being treated as resulting from over production of TNF-α or superoxide anion radicals. Since in view of the examiner's comments, the claims to treatment of organ damage are now limited to damage resulting from over production of TNF-α or superoxide anion radicals, specific reference to organ damage in these claims which already refer to conditions resulting from over production of TNF-α or superoxide anion radicals would be inappropriate.

We now turn to the rejection of the method claims under 35 USC 112. Two issues arise: the definitions of conditions to be treated and the definitions of the compounds used.

So far as the first is concerned, the conditions are now limited to rheumatoid arthritis (claim 14), Crohn's disease (claim 14), ulcerative colitis (Claim 14), liver damage (claims 18, 44, and 60), lung damage (claims 18, 44, and 60) and kidney damage (claims 18, 44, and 60),

diseases associated with overproduction of TNF-α (clams 31 44, 46, 52, and 54 or overproduction of superoxide anion radical (claim 31). The specification provides data for compounds of Formula I wherein X^1 is phenyl, X^2 is hydrogen, R^1 and R^2 are hydrogen and R^3 is the sodium salt of the SO_3^- ion and of the equivalent compound wherein R^3 is hydrogen.. These data show in Figs 1 - 9 and establish the efficacy of the tested compounds in treatment of a variety of conditions associated with over production of TNF-α or superoxide anion. It is therefore submitted that the definitions of the conditions set out in the claims are such that one skilled in the art would be enabled to treat them based on the information provided. Furthermore additional conformation of what one skilled in the art would understand from the present specification was submitted in response to the previous action.

All the statements on p. 24 of the specification are well supported from the literature cited in the Section of "Background of the Invention" on p. 4 to 25 and our additional literature supported in our response to previous Office Actions. These are pathological consequences which have been well documented in the literature reports. It is well known that an effect on one part of a biological system mayl affect the other parts of the system and produces one immediate response which further triggers next response and so on to create a chain reaction. This is particularly true in terms of cytokines (TNF-a is one of the key cytokines which will activate the release of superoxides and iNOS, the latter two can further activate the release of TNF-a to aggravate the situation or inflammatory response). These are facts and basic sciences that are foundation of today's biological sciences. Review of a patent application should be able to accommodate the discoveries of sciences.

1) Claim 14: Remicade, a TNF-a inhibitor (TNF-a: key to autoimmune disease), was approved by FDA for treating Crohn's Disease in 1998 and rheumatoid arthritis in 2000 and ulcerative colitis in 2005. Although ulcerative colitis is approved in 2005, the rationale and biochemical evidence is well known before 2000 that inhibition of TNF-a, which has been known a culprit for tissue injuries or organ injuries, can cure many diseases. However, the theory related to the treatment of disease is not necessary to correlate or to be validated by

FDA's approval which requires more than treatment of diseases such as regulatory issue and safety issues etc. Remicade clearly supports that inhibition of TNF-a can offer many therapeutic potentials.

A compound with a well-known mechanism related to diseases is taken granted to own certain known therapeutic potential. For examples, if a compound is shown to be a COX (cyclooxygenase) inhibitor in vitro, scientists or medicinal chemists will agree it will possess clinical utilities of known ibuprofen but no one will know if the compound can get an FDA's approval.

Organ Failure or pulmonary fibrosis: part of utility from TNF-a inhibition. Organ failure is the last phase of sepsis. Lung inflammation or lung damage can lead to pulmonary fibrosis. Effects in preventing organ failure due to severe septic shock will be the same as improvement of mortality of severe sepsis (also see the discussion below: Section 2 on Claims 18 and 60). To expedite the execution, those two indications have been deleted.

2) Claims 18 and 60: We have data to prove that the compound can prevent or treat liver damage (see Figures 5 and 6: reduction of SGPT and SGOT liver enzymes; elevation of these two liver enzymes is an indication of liver damage clinically), lung damage (See Fig. 9: histopathological studies and PMN infiltration index both suggests the improvement of lung damage). TNF-a is a known culprit of organ damage or tissue injuries, and animal studies indicates our class of compounds have ability to prevent the organ failure which usually means that liver, lung and kidney lose their function which lead to the immediate death (see Figure 12 of the provisional application USSN 60/453771 filed in 2003 prior to PCT filing). They support our claim on kidney damage.

3) Claims 31, 44, 45, and 53: See Section also the discussion of Claim 14 in Section 1 above). As a result of TNF-a inhibition, a very broad pathological conditions or diseases can be treated or prevented based **on the literature**, as cited in the application (p. 4) and others such as diabetes (insulin resistance), chronic hepatitis C, B etc. These are scientific discoveries or validation, everyone including the examiner should accept the facts.

Applicants just make use of these well-established knowledge in the literature for our claims. Drug companies need to use biochemical discoveries or mechanism as targets to do research and development work and apply for patents way before those drug candidates go to clinical trials. Without a patent, the applicants do not believe there is a drug called "Remicade" in the market place to treat Crohn's disease, rheumatoid arthritis, and colitis today.

4) Claims 46, 52 and 54: The afore-mentioned statements are applicable to support those three claims.

It is therefore submitted that one skilled in the art would understand that the specification enables one to treat all of the conditions specified in the claims.

The second issue under 35 USC 112 is whether one skilled in the art would be enabled to use all of the compounds specified in the claims for treating these conditions.

The applicants disagree with the examiner's rejection based on Lee's patent. Firstly, in contrast to examiner's statement that " Lee disclosed in Example 2 that of the eight flavone compounds tested, only oroxylin A inhibited LPS-induced COX2....", there is ONLY ONE FLAVONE COMPOUND (oroxylin A) instead of eight flavone compounds tested in Example 2. In Figure 1 of Lee's patent, there are 8 compounds and chemically they can be classified to **five groups of structurally diversified compounds**, as described below

Group 1 glycoside:

N1: Myricitrin, a 5,7-dihyroxyflavone **glycoside**

Group 2 flavone:

N2: Orxylin, a 5,7-dihyroxy-3-methoxy**flavone**

Group 3 Monosaccharide:

N3: Penta-O-galloyl-b-**glucopyranose (contain no flavone)**

Group 4 Disaccharide:

N4: Woodfordin C, a compound with two sugar units and two diphenyl phenyl ether **(contain no flavone)**

N5: Oenothein B, an analog of woodfordin

N6: Cuphiin D1, an analog of woodfordin

Group 5 xanthone:

N7: Emodin, a **xanthone** compound **(not a flavone)**

N8: Physcion, an analog of Emodine.

There is therefore no proper basis for the examiner's statement that Lee indicates a lack of predictability among flavones because only one of the compounds referred to is a flavone.

Therefore, everyone skilled in the art of Structural Activity Relationships (SAR), would say there is no basis for discussing SAR at all, as there is only one flavone compound described. Although the glycoside myricitrin (N1) contain an aglycon **5,7-dihyroxy**flavone, under in vitro conditions (as used in Lee's patent) it will not hydrolyze to 5,7-dihyroxyflavone. Besides, 5,7- dihyroxyflavone is different from the compounds **(5,6,7-trihydoxy**flavones) of the present application. Secondly, the patent basically uses one compound to claim so many utilities for so many analogs. Lastly, the applicants would like to point out that there are plenty of literature to support that organ damage can be resulted from cancer, infections, diabetes, exposure to alcohol and asthma as shown in the following examples briefly:

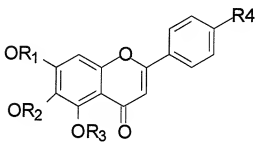
Liver cancer causes liver damage and patients need liver transplants;
Infections by hepatitis C virus (HCV) lead to hepatitis, liver fibrosis and cirrhosis (liver damage);
Diabetes will lead to insulin resistance which will lead to heart attack, fatty liver disease (leads to liver cirrhosis), eye damage, kidney damage;
Exposure to alcohol: alcohol will induce fatty liver disease ((leads to liver cirrhosis)
Asthma is one kind of lung damage; it is also called COPD (*chronic obstructive pulmonary disease* (*COPD*).

C. The existence of working examples

The background of Invention and Specification of our application, as discussed in Section 1 of the **Remarks**, spell out clearly the relevancy of diseases related to overproduction of TNF-a, superoxides and iNOS. In Lee's patent, they related their biochemical intervention to claim broad applications. The present claims are directed to utilities of baicalein analogs which are not claimed in the literature. Furthermore, correlation is nice to have scientifically and clinically, but in reality pathological conditions or diseases do not need correlation to have manifestation of the disease. For example, plasma levels of PSA (prostate specific antigen) have no correlation with prostate cancer, neither the enlargement of prostate state. Levels of plasma TNF-a concentration do have a correlation with liver damage.

D. Quantity of Experiments

Since examiner's statement that "there is no way to predict a priori" is based on a wrong assumption that Lee's patent used **8** flavone compounds in Figure 2, and we have 2 in vivo experiments plus in vitro TNF-a inhibition test on many new baicalein or 5,6,7-trihydroxyflaone derivatives which provide a nice and scientific structure-activity relationship (SAR), prediction should be easily made by one skilled in the art of SAR. In vivo experiments are expensive and also been restricted because of animal welfare protection issue. We used in vitro to substitute the in vivo test, as part of the trend in the drug research. In addition, two animal studies have been done already. Besides, there is a correlation between in vivo and in vitro TNF-a inhibition by baicalein (see additional data in vitro below; these data for some Excel data transfer reasons were not shown in our response of July 24, 2009) which supports our prediction.



TNF-a Inhibition in LPS-stimualted U937 cells

	% of inhbibition
R1=R2=R3=R4=H(Baicalein)	31% at 100 μM
R1=R2=R3=M3 R4=H	18% at 100 μM
R1=R3=H, R2=Me, R4=NH2	50% at 69 μM

It is therefore submitted that based on the known information one skilled in the art would be enabled to use any of the compounds set out in the claims for the treatments specified.

Now let us turn to the question of "R1 and R2" and "R2 and R3" together with the atoms to which they are bound form a methylenedioxy group. This is support by compounds in Example 1 of our PCT application, p. 35 lines 23 and 32; Preparation of 6,7-methylendioxy-5-hydroxy-4'methoxyflavone and 4'-[2-(N,N-diethylamino)ethoxy]- 6,7-methylendioxy-5-hydroxyflavone respectively. In addition, on p. 11 line 30, "heterocycle", as defined in the

original claim, is said "having one hetero atom, such as N, O, or S, within the ring". In response to previous objections to this definition, that applicants have limited it to the simplest possible heterocycle meeting the requirements of the formula as having two oxygen atoms and the only heterocylic group present in any specific compound mentioned in the specification. The simplest possible heterocycle contemplated by the original disclosure is a 5-membered ring heterocycle. The 5-membered ring contains 2 O atoms, the rest must be filled with carbon, as the basic rule of organic chemistry. The general disclosure must be regarded as teaching at least the simplest member of its group, especially when this structure is the only heterocyclic structure described in any specific compound. This disclosure of specific compounds clearly indicates that at the time of filing, the applicant was teaching that the heterocyclic structure at least included compounds wherein R^1 and R^2 or R^2 and R^3 and the oxygen atoms to which they are bound form a methylene dioxy group. It is therefore submitted that the requirements of 35 USC 112 have been met.

Turning now to the art-based rejections, it is noted that these have been raised only against any of the method of treatment claims.

Cassels does not cover baicalien analogs, (i.e, 5,6,7-trihydroxyfalavones but a variety of flavone derivatives in which the 5, 6, 7, 8 and 4' positions are preferably hydrogen, hydroxyl or halo and the most particularly preferred are those wherein the 5 substituent is hydroxyl or hydrogen, the 6-substituent halo, the 7-substituent hydroxyl or halo, the 8-substituemnt halo and the phenyl group is substituted by hydroxyl. Specific named preferred compounds are:

Compound	Substituent position				
	5	6	7	8	Phenyl substituent
Flavone	H	H	H	H	H
Chrysin	OH	H	OH	H	H
Apigenin	OH	H	OH	H	4-OH
2'-chlorochrysin	OH	H	OH	H	2-Cl
2'-fluorochrysin	OH	H	OH	H	2-F
6,8-dibromochrysin	OH	Br	OH	Br	H
7-bromo-flavone	H	H	Br	H	H

All of these lack an oxy link in the 6 position which is an essential feature of the applicant's claims. These are quite different structures from baicalein which constitutes a specific class

in terms of chemistry and pharmacology because of potential of hydrogen bonding properties and acidic hydroxyl proton. Presence of 3-adjacent hydroxyl groups provides a specific regioselective O-alkylation or de-alkylation at 5, 6, and 7-position of the baicalein moiety. Therefore. we disagree that all flavones should be treated as the same species, similar to what we can not say that aspirin (a salicylic acid analog) is the same as ibuprofen which is also a phenyl derivative with an acid group on the side chain.

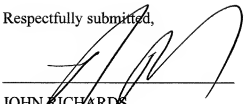
The examiner argues that Cassels disclosure goes beyond his specific compounds. This is true, but the nature of the specific compounds described is a proper guide to the breadth of his teaching. Cassels teaching is that the 6 position should preferably be halo substituted not substituted with an oxygen-containing group.(see column 2 lines 20 – 26). It is submitted that one skilled in the art would not regard Cassels as teaching any of the compounds claimed.

Furthermore Cassels describes compounds having **anxiolytic properties** which is not relevant to our claimed utilities such as liver damage, Crohn's Disease etc. which pharmacologically more related to cytokine inhibition and located in the peripheral system of human body. These types of diseases are quite different from anxiolytic properties which are mainly mediated from the central nervous system. There is therefore no reason why one skilled in the art would have thought to modify compounds selected for their anxiolytic properties to produce compounds useful for treatment of the conditions treatable by the compounds of the present invention. One skilled in the art would not relate anxiolytic with organ damage because of lack of scientific rationale or any link between two entirely different biological functions and systems. There is therefore no reason why one skilled in the art would seek to modify the compounds described to produce compounds having the structure and properties of the compounds of the present claims.

It is therefore submitted that all claims now meet the requirements of 35 USC 102 and 103.

In view of the foregoing, it is submitted that this application is in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,



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